REMARKS

Claims 37-56 were previously pending. Claims 37, 39 and 54 are currently amended. Claim 38 is canceled herewith. Claims 37 and 39-56 are pending with claim 37 being independent. No new claims have been added. No new matter is introduced.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claim 54 has been rejected under 35 U.S.C. 112, second paragraph as being indefinite resulting from a lack of antecedent basis. Applicants have amended claims 37 and 54 correct the antecedent basis problem. It is believed that he amendment is sufficient to overcome the rejection.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 37-56 have been rejected under 35 U.S.C. 112, first paragraph for lack of enablement. According to the Examiner, it would have required undue experimentation for one of skill in the art to practice the invention in view of the teachings of the specification, the unpredictability of the art and the lack of working examples.

Amended claim 37 recites a method for stimulating a subjects response to a vaccine by administering an immunostimulatory oligonucleotide having an unmethylated CpG dinucleotide and a phosphate backbone modification to the subject as a vaccine adjuvant in order to stimulate a response to the vaccine. The claim requires that both an oligonucleotide and a vaccine be administered. The vaccine must be administered in order for the oligonucleotide to stimulate the subjects response to that vaccine. The specification teaches that the oligonucleotide is administered in conjunction with the vaccine. "Preferably the unmethylated CpG dinucleotide is administered slightly before or at the same time as the vaccine."

The data and description in the patent application provide a teaching to those of skill in the art that CpG containing oligonucleotides can be used as immune stimulants. The specification teaches that oligonucleotides containing an unmethylated CpG dinucleotide activate lymphocytes and are thus useful for the treatment of disease and are useful as adjuvants when administered with a vaccine (Pages 7-8 and page 21 lines 18-21). The specification sets forth a description of the types

of oligonucleotides useful according to the methods of the invention (Pages 9-11), methods for making the oligonucleotides (Page s 20-21), modes of administration (Page 22 lines 12-15), and pharmaceutical carriers useful in the methods (Page 22 lines 17-25).

The specification also teaches that part of the invention involved the discovery that CpG containing oligonucleotides mimic bacterial DNA in their ability to promote an immune response. The inventors believed they discovered one of natures pathways fundamental to the immune system. This discovery is described on pages 19-20 of the specification under the heading "Teleological Basis of Immunostimulatory Nucleic Acids." It is taught that the stimulatory CpG motif, identified according to the invention, is common in microbial genomic DNA, but quite rare in vertebrate DNA. Experiments described in Example 3, in which methylation of bacterial DNA with CpG methylase was found to abolish mitogenicity, demonstrated that the difference in CpG status is the cause of immune stimulation by bacterial DNA. It is further taught that "Teleologically, it appears likely that lymphocyte activation by the CpG motif represents an immune defense mechanism that can thereby distinguish bacterial from host DNA.....*Since the CpG pathway synergizes with B cell activation through the antigen receptor, B cells bearing antigen receptor specific for bacterial antigens would receive one activation signal through cell membrane Ig and a second signal from bacterial DNA, and would therefore tend to be preferentially activated. The interrelationship of this pathway with other pathways of B cell activation provide a physiologic mechanism employing a polyclonal antigen to induce antigen-specific responses."* (emphasis added)

Additionally, The Examiner has stated that the specification is not enabling because the specification does not contain any working examples. Working examples are not necessary for enablement.[1] However, Applicants have provided numerous working examples in the specification. The data in the application, including that represented in Tables 1-3, establishes that the

[1] The MPEP section 2164.02 states: "An applicant need not have actually reduced the invention to practice prior to filing. In *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date, no person had built a light amplifier or measured a population inversion in a gas discharge. The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)). and "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)."

unmethylated CpG is responsible for the immune stimulation. Many oligonucleotides were tested. The data is consistent with the broad teachings of the invention that unmethylated CpG oligonucleotides stimulate an immune response, such as by activating B cells. The cumulative data set forth throughout the patent application strongly support the use of CpG oligonucleotides as adjuvants. For instance the following working examples are included in the specification: CpG oligonucleotide induced B cell activation as measured by ^{3}H uridine (proliferation) and IgM induction (Ab production) for instance, Table 1, Examples 1 & 2; CpG oligonucleotide induced IL-6 & IL-12 induction (*in vivo*) for instance, Example 6, paragraph spanning pages 16--17; CpG oligonucleotide induced increased MHC II cell surface induction (marker of B cell activation) for instance, page 17 lines 8-19 & Example 1; combination of CpG oligonucleotide and anti-IgM resulted in a 10 fold (synergistic) increase of lymphocyte activation for instance, data described in page 15 lines 8-18; and demonstration that CpG protects B cells (WEHI-231) against growth arrest or apoptosis induced by cross-linking of the receptor for instance, page 16 lines 21-30 & Example 7. *One of skill in the art would expect, based on these data, that CpG oligonucleotides are useful as adjuvants to stimulate an antigen specific immune response to a vaccine.* These examples correlate with the claimed method. When viewed together these examples teach one of skill in the art that unmethylated CpG oligonucleotides are useful for stimulating an antigen specific immune response. These data led the inventors to conclude that CpG oligonucleotides functioned, like bacterial DNA, by inducing B cell activation to provide a physiologic mechanism employing an antigen to induce antigen-specific responses (under the section entitled "Teleological Basis" and described above).

The Examiner has asked in the Office Action on page 3 whether the Experiment of Example 5 was actually performed. Applicants confirm that it was performed and the data was described in the specification on page 17 lines 9-24.

The Examiner has cited several papers, all of which have a publication date later than Applicants filing date, in support of the lack of enablement rejection and in particular in support of the argument that the state of the art at the time of the invention was unpredictable.

The Examiner has cited Threadgill et al (Vaccine 1998, 16:76-82) for the proposition that CpG oligonucleotides do not function as adequate vaccine adjuvants for bacterial polysaccharide

vaccines. A pointed out in response to the prior office action, although Threadgill et al report that CpG oligonucleotides are not useful adjuvants for polysaccharides, their key conclusions have since been refuted by other investigators. Recent reports using "normal" doses for vaccinating mice and assaying for IgG show adjuvant effects, even with a variety of polysaccharide antigens, especially when they are formulated or conjugated. References addressing these issues were discussed in Applicants prior response.

The Examiner has confirmed that some references (Gallichan et al 2001 and Harandi et al 2004) have demonstrated that CpG functions as an adjuvant in some viral compositions. The Examiner, however, states that these teachings are not indicative of the enablement at the time of the invention. This position is inconsistent. The Examiner has cited post-filing references to demonstrate that the invention was unpredictable at the time the application was filed. Post filing references may also be used by Applicant to rebut the Examiner's assertion that the invention was unpredictable by demonstrating that the claimed invention is functional as described by Applicant in the patent application.

McCluskie et al 1999 (Molecular Med. 1999, 5/5:287-300) and Krieg et al 2000 (Immunology Today 2000, 21/10:521-526) have been cited for the proposition that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism.

McCluskie et al is an article describing DNA vaccines against Hepatitis B virus. On page 296, the page identified by the examiner, the reference mentions that one of the factors involved in influencing the Th bias of the response to DNA vaccines is the presence of CpG motifs. The reference is not relevant to the enablement of the pending claims because the claims as amended do not encompass plasmid vectors (or DNA vaccines). The pending independent claims are directed to the use of oligonucleotides having a phosphate modified backbone. The issues of predictability and therapeutic effectivity are very different for CpG oligonucleotides and DNA vaccines.

The Examiner has indicated that the claims as written encompass DNA vaccines. Applicants disagree because the claims are directed to oligonucleotides, which do not encompass DNA vaccines. Applicants have amended the claims, however, to include the limitation that the

oligonucleotide encompasses a phosphate modified backbone. DNA vaccines generally do not include phosphate modified backbones.

Krieg et al is a review article describing the uses of CpG oligonucleotides. The office action specifically points to page 524 of the reference in support of the examiner's argument that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism. Applicants do not see this teaching in the reference. In fact the reference teaches on page 524 that "Unlike many vaccine adjuvants that have been extremely effective in mice but disappointing in humans, CpG DNA is also highly effective in higher primates." This teaching does not support the examiner's assertion that the administration of CpG oligonucleotides varies depending on the organism. Furthermore, Krieg et al describe the usefulness of CpG oligonucleotides in producing a Th1 biased immune response. Page 524 of Krieg et al includes the following teaching:

> "These and subsequent studies have shown CpG DNA to be a more effective Th1-like adjuvant than complete Freund's, and to be effective with multiple types of antigens and routes of immunization including mucosal immunization (reviewed in Ref. 50). In fact, in a comparison of 19 different adjuvants, CpG DNA was found to be the strongest for inducing Th1-like immune response to tumor antigens[51]"

The Examiner has cited Wohleben et al (TRENDS in Immunology, 2001 22/11:618-626) in support of 2 arguments: 1) that the "state of the art questions whether 'CpG-ODNs can be used in humans to inhibit the development of asthma?'" and 2) that Wohleben teaches that "all approaches that induce Th1 responses have the potential side-effects of Th1cell-mediated inflammation potentially causing serious tissue damage." The applicants respectfully disagree with the Examiner's characterization of the reference.

The pending claims do not encompass a method for treating asthma. Regardless, Wohleben et al actually provides a favorable view of CpG oligonucleotides and their usefulness in the treatment of asthma. The use of CpG oligonucleotides is identified in the abstract and conclusion of the paper as one of "the most promising approaches" for the treatment of atopic disease and particularly asthma. Even the cited paragraph on page 620 relates to the expectation that CpG

oligonucleotides will be effective in humans. It is taught that the "results obtained from animal models suggest that it is probable that these approaches might also be successful in humans to reduce the development of atopic disorders." (Page 620 second column first paragraph, emphasis added) and "This suggests that the treatment of humans with CpG-ODNs could be very effective in inhibiting the development of asthma." (Page 620 second column first paragraph). Thus, the teachings found in Wohleben et al are not sufficient evidence that the invention was not enabled at the time of filing of the patent application.

Further, the teachings of Wohleben et al with respect to potential side effects do not support a lack of enablement of the claims. Wohleben et al teach on page 620 immediately following the discussion of side effects that "it is totally unclear if this can also occur in healthy rodents or, more importantly, humans." (Page 620 second column first paragraph). Additionally the issue of whether a drug is safe and has no side effects is not an appropriate test for enablement. MPEP2164.01(c). "The applicant need not demonstrate that the invention is completely safe." In fact, one cannot possibly determine the parameters of safety without a controlled clinical trial, and it is well established that a clinical trial is not required for enablement.

Furthermore, the Wohleben et al reference, as well as the others cited for safety concerns and discussed in more detail below, do not suggest that use of CpG would be unsafe. All drugs have some side effects. The references at best suggest that care should be taken to see if there may be certain patients for which the compound might be contraindicated. This is the type of inquiry made by those of ordinary skill in the art respecting all drugs. There is no evidence in any of the cited papers that CpG oligonucleotides would be unsuitable for use as an adjuvant. To the contrary, the cited papers, published years after the filing date, continue to support the view that CpG oligonucleotides should be advanced through clinical trials for use as adjuvants. One of ordinary skill in the art would have believed, based on the data in the application, that CpG oligonucleotides would be well suited as clinical trial candidates for use as adjuvants. The papers cited for safety issues have not altered that view.

The Examiner has cited the Kline et al 2002 (Am. J. Physiol. Lung Cell Mol. Physiol., 2002, 283:L170-L179) and Kline et al 1998 (J Immunol 1998, 160: 2555-2559) references to demonstrate

that the use of CpG alone in some instances is not effective for the treatment of asthma. Applicants reiterate that the pending claims are not directed to the use of CpG oligonucleotides to treat asthma. However, since the references were made of record, Applicants address the rejection. The Examiner asserts that Kline 2002 teaches that a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in this animal model. The section of the paper identified by the Examiner on page L172 relates to an experiment designed to model "persistent asthma in humans, who, by current standards of treatment, require intensive anti-inflammatory therapy." The claimed invention does not require that any form of asthma, including persistent asthma be treated with a single dose of CpG. Doses are within the purview of those skilled in the art, and the data in the paper supports that monotherapy at appropriate doses can work. In fact, many drugs including other drugs for treating chronic asthma are not effective as a single dose.

The Examiner has also indicated that Kline 2002 teaches that "splenocytes from OVA-treated mice did not develop an antigen specific Th1 phenotype. However mice treated with CpG ODN and OVA had a marked shift toward a Th1 response to antigen as well as reduction in airway eosinophilia, serum IgE and bronchial hyperreactivity (p. L176, col. 2)." (Office Action page 9). This statement does not support a lack of enablement of the claimed invention. The lack of development of a Th1 phenotype in mice in response to OVA treatment is not inconsistent with the invention. The fact that CpG oligonucleotides produced a shift towards a Th1 response is consistent with Applicants' findings.

Weiner (J. Leukocyte Biology, 2000, 68:456-463) is cited for the proposition that the molecular mechanism of CpG is unknown. Knowledge of the mechanism of action isn't necessary, particularly in view of the detailed knowledge at the time the patent application was filed of the cellular effects of CpG oligonucleotides. The patent application identifies consistent changes in the immune system at the cellular level that occur in response to CpG administration and which are therapeutically relevant. Additionally, Table 1 of Weiner lists examples of cellular effects arising from immunostimulatory CpG ODN. A lack of understanding of the molecular mechanism does not render the cellular results unpredictable. Other statements in Weiner are consistent with

enablement of the claimed invention. For instance it is taught on page 456 1st column second full paragraph that "Studies to date suggest CpG DNA could have significant therapeutic promise in the treatment of a variety of disorders, including infectious disease, allergy, and cancer." Page 457 under "In vivo effects of CpG ODN" teaches that "extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed *in vivo* data fits well with the *in vitro* data outlined above."

Agrawal et al (Molecular Med. Today 2000, 6:72-81) has been cited in support of the assertion that the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable. In particular, the examiner has identified pages 78-80 as being particularly relevant. Agrawal et al is a review article describing antisense oligonucleotides. The authors suggest on page 78 that in order to *reduce* non-antisense related activity it is best to avoid CpG motifs. The authors also indicate that if it is not possible to avoid CpG motifs, then it is possible to make one of 3 modifications to reduce the CpG activity of the oligonucleotide. One of the suggested modifications is to replace the cytosine base of the CpG with a 5-methyl cytosine base. The instant specification teaches that a CpG containing oligonucleotide has an unmethylated C in the CpG motif. Further, the cited section of Agrawal et al teaches that the proposed 3 modifications "significantly reduced side effects". Agrawal et al does not teach that immune stimulation was abolished with any of these proposed modifications, just reduced.

Hussain et al., was cited for the teaching that long term benefits of CpG therapy in allergic rhinitis are speculative. A copy of the Hussain et al reference and the complete citation were not included in the office action. Thus, Applicants cannot address the merits of the full reference. Applicants note, however, that the claimed invention is not directed to the treatment of allergic rhinitis. Thus, a teaching that use of CpG therapy in the treatment of allergic rhinitis is speculative is not relevant to the claimed invention.

Satoh et al. (Fukushima Igaku Zasshi 2002, 52/3:237-250) was cited in order to demonstrate that CpG was associated with dangerous side effects. The Satoh et al. reference is an abstract describing a study on the effects of CpG oligonucleotides administered subcutaneously to mice that are treated with DNFB. It was concluded that CpG oligonucleotides were responsible for worsening

of the allergic contact dermatitis (ACD) induced by DNFB. As mentioned above with respect to Wohleben et al the issue of whether a drug is safe and has no side effects is not an appropriate test for enablement. Additionally, the teachings of the Satoh et al reference are not sufficient to establish a lack of enablement for the claimed invention. The ACD is caused by DNFB treatment. The fact that CpG oligonucleotides may contribute to type IV hypersensitivity responses initiated by DNFB does not establish that CpG oligonucleotides would cause ACD in the absence of DNFB.

Dziadzio et al (Handbook of Experimental Pharmacology 161:273-285, 2004) and Metzger et al (J. Allergy. Clin. Immunol. (104)2 Pt. 1:260-266, 1999) are both cited for the teaching that CpG ODN therapy has yet to be demonstrated in human clinical trials. Both references however summarize effects of CpG ODN, in *in vitro* and *in vivo* murine systems, which parallel those required for human therapy. Neither reference doubts that CpG ODN will be effective in humans. Dziadzio et al actually teaches that CpG ODN are encouraging as potential therapies for allergic disease. After summarizing several sets of data on page 280, Dziadzio et al teach:

> "These data suggest that ISS-ODN can induce a Th1 phenotype prior to allergen exposure. It appears that even without the presence of allergen, CpG motifs can induce a Th1 phenotype in multiple cell types including B cells, antigen-presenting cells (macrophages, dendritic cells), T cells, and NK cells. The expression of Th1 cytokines along with an upregulation of costimulatory molecules on these cells underscores the importance of ISS-ODN in Th1 and innate immune responses. The persistence of a Th1 response after antigen challenge in sensitized mice is encouraging as potential therapy for allergic disease." (page 280, 2nd-3rd full paragraphs).

The teachings of the references as a whole do not support a finding that the claimed invention was unpredictable at the time of filing of the patent application.

The Examiner has cited Van Uden et al (J. Allergy Clin. Immunol., 1999, 104:902-910) for the concept that each ISS has a minimum length limitation and that potential side effects associated with treatment must be considered. With respect to the section of the paper that refers to the length of ODN, the authors do not conclude that there is a specific rule for the length of the ODN. The authors hypothesize that different lengths and flanking sequences have an impact on the activity of the ODN. The patent application as filed confirms that certain motifs and lengths are preferred.

However, it is believed that most unmethylated CpG containing oligonucleotide within the scope of the claims would have the ability to initiate *in vivo* a pattern of cytokine release which would drive the immune system toward a Th1 response when administered in an appropriate dosage.

The examiner quotes some language from page 907 column 2 and page 908 column 1 related to the issue of side effects associated with CpG oligonucleotide administration. Each of these statements, however, is taken out of context. After the quoted section the authors point out that such side effects have not been observed. For example, the Examiner has pointed to the statement on page 907 that "There is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers" and compared the effects of CpG with LPS (Office Action page 11). In contrast to the implications from the language quoted in the office action, immediately following that paragraph the authors conclude

> "Although these reports demonstrate the possibility of shock in extreme cases of sensitization or concurrent LPS exposure, there has never been a reported case of ISS alone causing shock in any kind of healthy animal at any dose." (Page 908 column 1 lines 2-6) and
> "We and others have never observed gross inflammation in response to ISS in ODN or plasmid form in any experimental animals or humans." (page 908 first column first full paragraph)

The Examiner has also stated that Van Uden et al teaches that "ISS could cause excessive local inflammation as seen with other powerful Th1 adjuvants, such as CFA." In contrast to this statement the authors point out an experiment in which bacterial DNA complexed with CFA is injected into mice. It is concluded that

> "When the mixture is given to preautoimmune NZB/NZW F1 mice, they develop antibodies that cross-react with mammalian DNA, but surprisingly they are actually protected from their spontaneous autoimmune disease. There still are no examples of ISS directly causing any type of autoimmune disease in animal models." (page 908 paragraph bridging columns 1 and 2).

Kussebi et al., Curr. Med. Chem. – Anti inflammatory & Anti-Allergy Agents, 2003, 2: 297308 was cited for the teaching that direct conjugation of CpG-ODNs to allergenic proteins or

peptides was more effective than their co-administration. Applicants did not receive a copy of the full reference. The teachings of the cited portion of the reference, however, do not render the claimed invention unpredictable. Simply because the authors found CpG conjugated to an allergen to be more effective than CpG administered separately from an allergen does not suggest that the claimed invention is unpredictable. The claimed invention encompasses the use of a CpG oligonucleotide with a vaccine antigen, whether or not the components are conjugated.

In addition to the discussion of safety issues raised with respect to the cited references, Applicants point out that Several Phase I and II studies have been performed in humans to date. For instance, subcutaneous administration, like that in the Satoh reference, has been performed in humans for a cancer trial. The data are described in Kim et al., Blood, volume 4, issue 11, abstract # 743, Nov. 16, 2004. Toxic effects that would halt further human trials were not observed, even though the patients were provided CpG oligonucleotides in very aggressive doses. The abstract concludes that "weekly doses up to 0.36 mg/kg have been well tolerated." The results of this clinical trial are submitted herein to demonstrate that CpG oligonucleotides have been safely administered to humans, and not to demonstrate efficacy of the compounds. This clinical trial demonstrates that CpG oligonucleotides have been administered to humans and were well tolerated.

Several additional Phase I and II studies demonstrate that CpG ODN are well tolerated in human subjects as well as the efficacy of CpG ODN in stimulating immune responses in such subjects. (See for example Creticos et al, Immunotherapy with immunostimulatory oligonucleotides linked to purified ragweed Amb a 1 allergen: effects on antibody production, nasal allergen provocation, and ragweed seasonal rhinitis, J Allergy Clin. Immunol. 109(4), 742-743. 2002; Simons et al, Selective immune redirection in humans with ragweed allergy by injecting Amb a 1 linked to immunostimulatory DNA, J Allergy Clin Immunol 113, 1144-1151 (2004); Krieg et al, Induction of systemic Th1-like innate immunity in normal volunteers following subcutaneous but not intravenous administration of CPG 7909, a synthetic B-class CpG oligodeoxynucleotide TLR9 agonist, J Immunother. 27, 460-471 (2004); Cooper et al, CpG 7909, an immunostimulatory TLR9 agonist oligodeoxynucleotide, as adjuvant to Engerix-B HBV vaccine in healthy adults: A double-blind Phase I/II study, J Clin. Immunol 24, 693-702 (2004); Halperin et al, A phase I study of the

safety and immunogenicity of recombinant hepatitis B surface antigen co-administered with an immunostimulatory phosphorothioate oligonucleotide adjuvant, Vaccine 21, 2461-2467 (2003); Siegrist et al, Co-administration of CpG oligonucleotides enhances the late affinity maturation process of human anti-hepatitis B vaccine response, Vaccine 23, 615-622 (2004); Cooper et al, Safety and Immunogenicity of CpG 7909 Injection as an Adjuvant to Fluarix Influenza Vaccine, Vaccine 22, 3136-3143 (2004); Speiser et al, Rapid and strong human CD8(+) T cell responses to vaccination with peptide, IFA, and CpG oligodeoxynucleotide 7909, J Clin. Invest 115, 739-746 (2005); van Ojik et al, Phase I/II study with CpG 7909 as adjuvant to vaccination with MAGA-3 protein in patients with MAGE-3 positive tumors, Ann.Oncol.13, 157. 2003.)

As described above, numerous working examples were provided in the specification. These examples in combination with the description in the specification were sufficient to enable one of skill in the art to practice the invention over the full scope of the claims. Consistent with the descriptions, a number of studies published since the filing of the patent application have reiterated, as set forth in the specification, that CpG oligonucleotides are useful as adjuvants. Several of the clinical trials described above, Cooper et al, Halperin et al, Siegrist et al, Speiser et al, and van Ojik et al, have demonstrated, as described in the specification, that CpG oligonucleotides, when administered with a vaccine to a human, produce an antigen specific immune response.

Thus, one of ordinary skill in the art, based on the teachings in the patent application, would have reasonably expected the claimed invention to work over the full scope of the claims.

Rejections Under 35 U.S.C. §102(b)

The rejection of claims 37 and 46-54 under 35 U.S.C. 102(b) as being anticipated by Tokunaga et al. has been maintained. Although, Applicants disagree with the rejection as set forth in more detail below, Applicants have amended claim 37 to incorporate a limitation of claim 38, which is currently not rejected, in order to advance prosecution. It is respectfully requested that the rejection be withdrawn.

According to the Office Action page 14, the rejection has been maintained and Applicants' arguments found not persuasive because Tokunaga et al describe the use of immunostimulatory

palindrome containing oligonucleotides as immunopotentiators. According to the Examiner "Dorlands Medical Dictionary defines an immunopotentiator as an agent that specifically or non-specifically enhances or augments the immune response, such as an adjuvant." Immunopotentiator is a broad term encompassing many different compounds. Although adjuvants may be one type of immunopotentiator, not all immunopotentiators are adjuvants. In the absence of any further indication in Tokunaga et al., that the compounds described therein are useful as adjuvants for stimulating an antigen specific immune response, one of skill in the art would not be led to the conclusion that such immunopotentiators are useful as adjuvants.

The Examiner has requested that Applicants identify co-pending patent applications that may be related to the claimed invention. Applicants will file an additional information disclosure statement updating the list of co-pending patent applications.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

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Respectfully submitted,

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